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REVIEW | *General Interest*

Carotid body: a metabolic sensor implicated in insulin resistance

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Conde SV, Sacramento JF, Guarino MP. Carotid body: a metabolic sensor implicated in insulin resistance. *Physiol Genomics* 50: 208–214, 2018. First published January 26, 2018; doi:10.1152/physiolgenomics.00121.2017.—The carotid body is now looked at as a multipurpose sensor for blood gases, blood pH, and several hormones. The matter of glucose sensing by the carotid body has been debated for several years in the literature, and these days there is a consensus that carotid body activity is modified by metabolic factors that contribute to glucose homeostasis. However, the sensing ability for glucose is still being pondered: are the carotid bodies low glucose sensors or, in contrast, are they overresponsive in high-glucose conditions? Herein, we debate the glucose and insulin sensing capabilities of the carotid body as key early events in the overactivation of the carotid body, which is increasingly recognized as an important feature of metabolic diseases. Additionally, we dedicate a final section to discuss new outside-the-box therapies designed to decrease carotid body activity that may be used for treating metabolic diseases.

carotid body; carotid sinus nerve; glucose; insulin; Type 2 diabetes

CAROTID BODIES IN THE PATHOGENESIS OF METABOLIC DISEASES

Obesity, metabolic syndrome, and Type 2 diabetes are a world pandemic affecting millions of individuals (23, 56a). Lifestyle changes, particularly sedentary life and hypercaloric diets, have indisputably contributed to the increasing incidence of these diseases (23, 56a). Despite the combination of antidiabetic therapies and/or insulin treatment, a considerable proportion of patients with metabolic diseases remain poorly controlled (16), a fact that has propelled research in metabolic disease pathophysiology and novel therapeutic targets that may contribute to increase patient quality of life.

Carotid bodies have been recently implicated in the pathogenesis of metabolic diseases (for reviews see 8, 9). These small organs, which sit bilaterally at the bifurcation of the common carotid artery, are multimodal sensors that detect biochemical substances in arterial blood. In fact, its location favors its nature as a major sensor in the control of the chemical composition of blood before it reaches the brain, which is highly dependent on oxygen and nutrients, mainly glucose, to function properly. The information detected by the carotid bodies is transmitted to the nerve terminals of the carotid sinus nerve (CSN), which, by reflex action, adapts the functional activity of efferent organs. The classical stimulus for the carotid body is hypoxemia, which leads to an increase in CSN activity that is integrated in the brain stem to induce succeeding cardiorespiratory reflexes aimed, primarily, to normalize the altered blood gases via hyperventilation and to regulate blood pressure and cardiac performance via sympathetic nervous system (SNS) activation (22, 28). More recently carotid bodies have been suggested also to perform metabolic sensing functions, responding to blood glucose and insulin (39). The emerging information on the role of carotid bodies as insulin and glucose sensors stands, naturally, on their anatomic location and crucial role as an alarm mechanism to the central nervous system in acute emergency situations that may lead to neuroglycopenia.

The carotid bodies have also been implicated in the pathogenesis of chronic pathophysiological conditions associated with metabolic disturbances that occur in the absence of hypoxia or hypoglycemia, such as Type 2 diabetes, hypertension, and chronic heart failure. Its role seems to be primordial in the initiation and maintenance of the core features of the diseases because CSN denervation or carotid body ablation causes remission of pathological manifestations (1, 13, 27, 31–33, 42, 45).

Surgical resection of the CSN has been shown both to prevent the development of insulin resistance and glucose intolerance in rats exposed to hypercaloric diets and to reverse pre-established dysmetabolism in animal models (42, 45). The favorable impact of turning off carotid body signaling in metabolic diseases is linked to restoration of sympathetic nerve overactivity to physiological levels (42, 45). Chronic cardiometabolic diseases like Type 2 diabetes, congestive heart failure, arterial hypertension, and obesity have long been known to occur in a setting of unrestrained sympathoexcitation, and recent evidence suggests that carotid bodies are overactive in these pathological conditions, driving an in-

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creased sympathetic tone, at least in some patients (10, 20, 38, 40, 47, 49, 50, 54). Limiting carotid body-mediated SNS activation exerts direct beneficial impact on hemodynamic parameters and on insulin signaling in insulin-sensitive tissues: increasing glucose uptake by the liver and visceral adipose tissue (45) and decreasing hepatic glucose production. These findings strongly suggest that the carotid body function extends beyond blood gas sensing and that carotid body dysfunction may be intimately related with the pathogenesis of cardiometabolic diseases.

TRIGGER: BITTER OR SWEET?

The hallmarks of metabolic diseases are peripheral insulin resistance, abnormal hepatic glucose metabolism, and progressive pancreatic beta-cell failure. All these characteristic features lead to a deterioration of glucose control progressively over time, leading to hyperglycemia, the core feature of metabolic diseases.

Recent evidence points to the existence of overactive carotid bodies in diseases where hyperglycemia is an important clinical hallmark, like Type 2 diabetes, sleep apnea, or metabolic syndrome (42, 45). A set of pertinent questions arise from this observation: are the carotid bodies overactivated by high-plasma glucose levels? Are the carotid bodies able to sense alterations in blood glucose levels? Are the carotid bodies glucose sensors?

In the last decade, several authors dedicated their research efforts to clarify these questions, focusing initially on the responses of carotid bodies to an acute situation of hypoglycemia. While the initial reports supported a role for carotid bodies as low-glucose sensors (34), subsequent studies strengthened the hypothesis that carotid sinus nerve activity is not modified by low glucose. Using freshly isolated intact rat carotid body preparations Conde et al. (7) demonstrated that the release of catecholamines from chemoreceptor cells was identical in the presence of physiological (5.55 mM) and low-glucose concentrations (3, 1, and 0 mM). Also, the authors showed that both the release of ATP from the carotid body and the CSN action potential frequency were unaffected by low glucose (7). These results support the notion that low glucose is not a direct stimulus for rat carotid body chemoreceptors (7), confirming previous results in the intact carotid body-CSN preparation performed by Almaraz et al. (2) in 1984 and by Bin-Jaliah et al. (5). More recently, Shirahata et al. (46) also confirmed the lack of effect of hypoglycemia in CSN activity, both in basal conditions and in response to hypoxia.

In contrast, Pardal and López-Barneo described increased sensitivity of chemoreceptor cells to low glucose, as hypoglycemia in carotid body slices inhibited K^+ currents and increased catecholamine release (34). Also, Zhang et al. (57) found an increased afferent action potential frequency in petrosal ganglions in cocultures of petrosal ganglions with carotid body chemoreceptor cells. The different low glucose concentrations and P_{O_2} values used in the different studies, as well as the type of preparation (intact preparation vs. cocultures or slices) where chemosensory cells may change their phenotype, have been used as putative hypothesis to explain the divergent results (21).

Recently, it was suggested that adrenaline, rather than low glucose, is the stimulus sensed by carotid bodies during hypoglycemia, that is responsible for carotid body-mediated changes in ventilation and CO_2 sensitivity during hypoglycemia. In vivo, a rapid fall in glucose induces a counterregulatory response that involved the release of several hormones, including adrenaline and glucagon, to restore blood glucose levels (Fig. 1). Thompson et al. (51) observed that the effects on minute ventilation and CO_2 sensitivity induced by hypoglycemia in Wistar rats were abolished by either β-adrenoceptor blockade or adrenalectomy. It was also demonstrated that physiological levels of adrenaline mimicked the hypoglycemia effect on ventilation and CO_2 sensitivity, providing evidence for a role of this counterregulatory hormone in the ventilatory response to hypoglycemia, as opposed to a direct action of low glucose on the carotid bodies (51). Bin-Jaliah et al. (5) observed a carotid body-dependent increase in ventilation in low-glucose conditions in the rat based upon the effect of CSN denervation to blunt the increased minute ventilation and rate of O_2 consumption ($\dot{V}_{O_2}$) produced by insulin-induced hypoglycemia. However, baseline chemoreceptor discharge frequency, recorded in vitro, was not affected by hypoglycemia

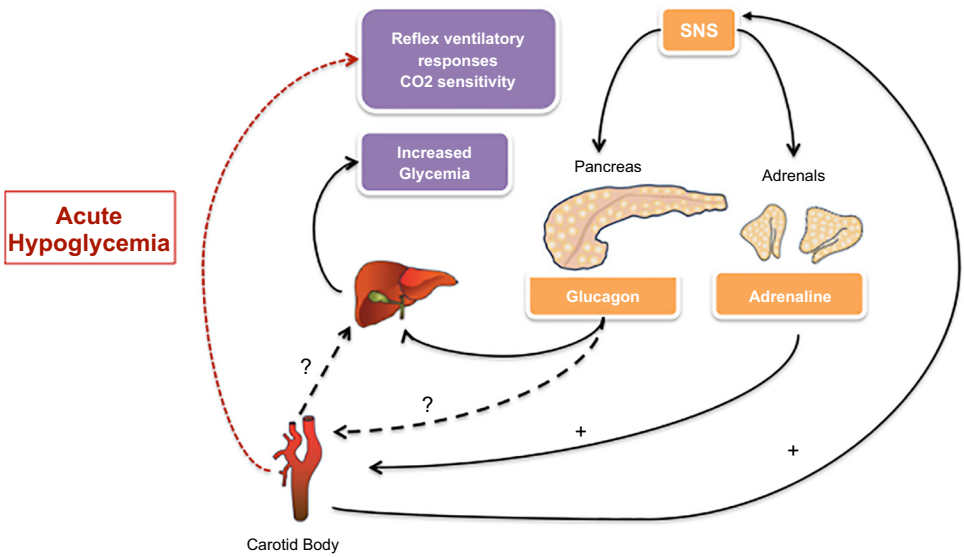

Fig. 1. Schematic representation of the hypothesis for the effect of acute hypoglycemia on the reflex ventilatory responses and CO_2 sensitivity mediated by the carotid body. SNS, sympathetic nervous system.

and did not increase when glucose was lowered from 10 to 2 mm. The results led the authors to propose that these changes are due to modifications in a metabolically derived blood-borne factor rather than glucose per se.

Altogether, the data do not support a sustainable role for chemoreceptor cells as glucose sensors and oppose the hypothesis that the carotid body belongs to a set of peripheral glucose sensors, like the ones existing in the pancreas or in the liver, that initiate reflex responses when plasma glucose levels fall below the physiological range. However, there is undoubtedly a link between carotid body activity and the regulation of glucose homeostasis, demonstrated by observational evidence.

Stimulation of carotid body induces a reflex hyperglycemia (37) and increases the hepatic glucose output (3), given that these effects are blocked by CSN denervation (3). Additionally, carotid body resection has been shown to blunt the counterregulatory responses to hypoglycemia induced by the hypoglycemic hyperinsulinemic glucose clamp, both in animals (25) and in humans (56). Thus, although some of the conclusions drawn from the above mentioned studies refer to low-glucose as a potential stimulus for carotid bodies, it should be noted that, in a significant number of in vivo animal and human studies, hypoglycemia was generated using high dose insulin infusions. Evidence demonstrates the existence of insulin receptors at the carotid body, and that insulin can induce a neurosecretory response at carotid body chemoreceptors cells, measured as increased intracellular calcium levels, release of ATP and catecholamines (42) and by insulin-driven increase in ventilation (42, 55). Additionally, it is documented that insulin drives sympathoexcitation (24), an effect that is mediated by its action on the arcuate and paraventricular nucleus in the central nervous system (for a review see 12), but also by the periphery, since injection of insulin into the carotid artery of anesthetized dogs produces an increase in blood pressure and sympathetic activity higher than systemic insulin administration (36). Taken together, these observations confirm the hypothesis that insulin is a stimulus for carotid body activation, independent of glucose levels and shift the paradigm of carotid body stimulus from "low glucose" to "high insulin" as the most important trigger for carotid bodies, in terms of glucose homeostasis control.

However, this paradigm shift does not respond to the initial question posed in this section: what about hyperglycemia?

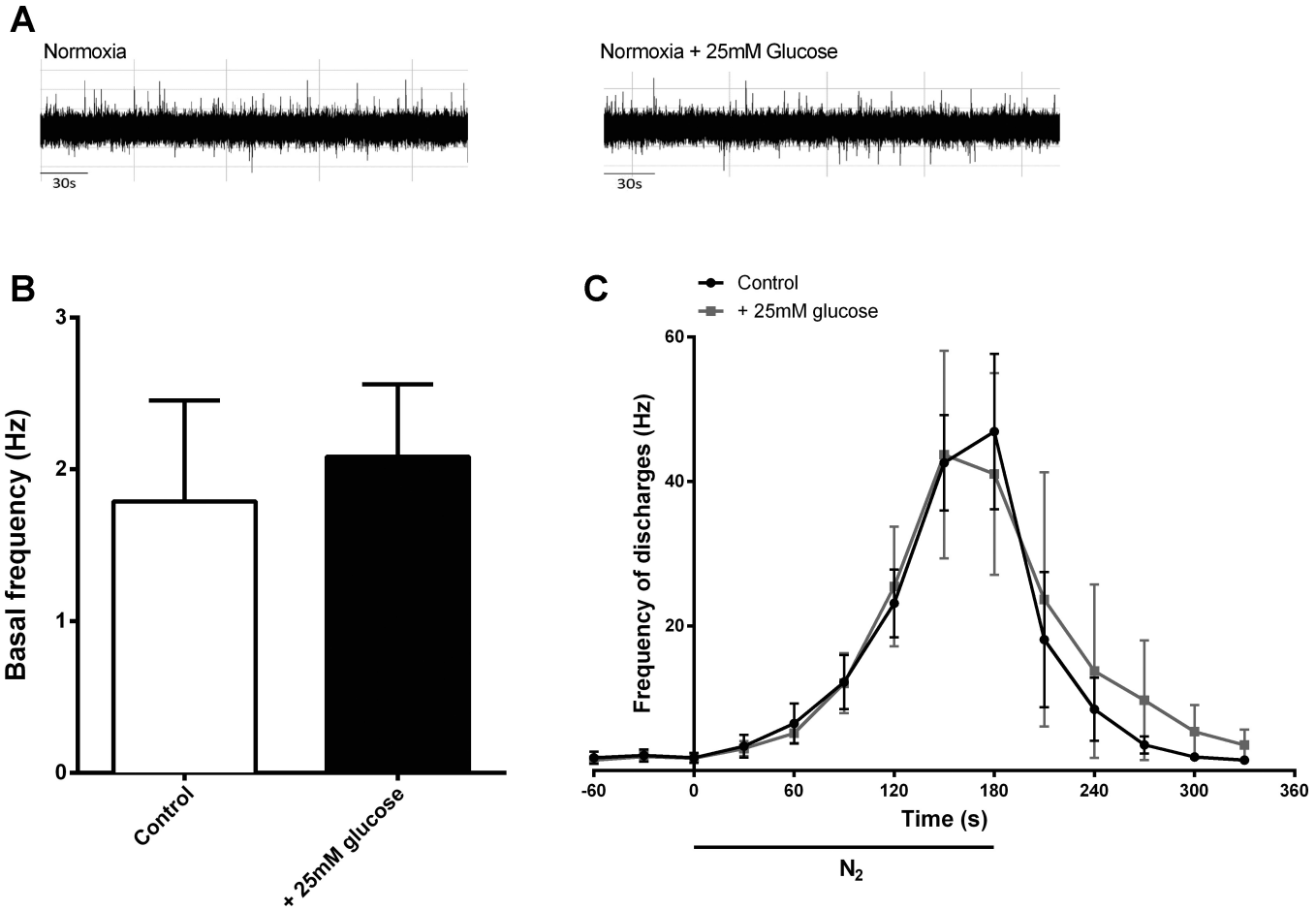

Fig. 2. Effect of hyperglycemia (25 mM of glucose) on rat carotid sinus nerve (CSN) chemosensory activity recorded ex vivo. *A*: typical neurograms for the effect of 25 mM of glucose on the basal frequency of action potentials of CSN. *B*: mean basal frequencies of the CSN chemosensory activity in the presence and absence of 25 mM glucose. *C*: area under the curve for the effect of hyperglycemia (25 mM of glucose) on the frequency of action potentials of CSN during superfusion with a solution equilibrated in response to 0% O_2 (N_2) in control animals. CSN recordings have been performed in an ex vivo carotid body-CSN preparation. The protocol for the study of the effect of hyperglycemia (25 mM glucose) on the basal and hypoxia CSN activity has been investigated while superfusing the preparations with solutions equilibrated with normoxia (20% O_2) during 5 min and with hypoxia (0% O_2) during 3 min. Data represent means ± SE.

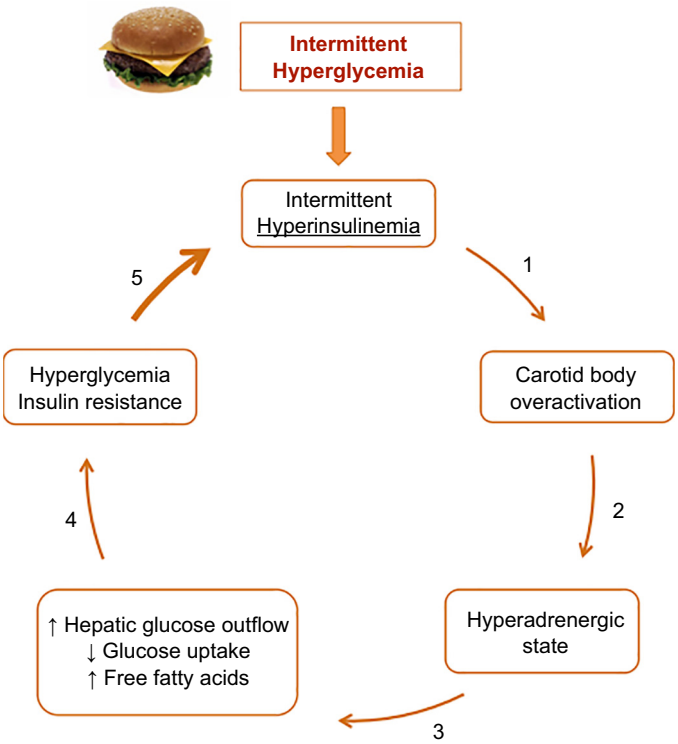

Fig. 3. Schematic of the vicious cycle initiated by hypercaloric diets that leads to the development and maintenance of metabolic diseases. Hypercaloric diets promote intermittent and high insulin release from the pancreas, which stimulates the carotid body to activate the sympathetic nervous system. The sustained overactivation of the carotid bodies/sympathetic nervous system results in an increase in free fatty acids as well as an increased hepatic glucose outflow that occurs concomitantly with decreased glucose uptake by the liver and the adipose tissue promoting insulin resistance that culminates in hyperglycemia.

Are carotid bodies able to sense hyperglycemia and respond to hyperglycemia in a setting of insulin resistance as occurs in early metabolic diseases development? Or is hyperinsulinemia responsible for the metabolic vicious cycle of sympathoexcitation and insulin resistance?

To test the hypothesis that hyperglycemia stimulates carotid bodies, we evaluated the effect of 25 mM of glucose on the chemosensory activity of the CSN, which measures the output of the carotid body in normoxia and hypoxia. The activity of the CSN was recorded ex vivo in the isolated rat carotid body-CSN preparation. We found that hyperglycemia (25 mM of glucose) did not modify either the basal action potential frequency (Fig. 2, *A* and *B*) or the CSN chemosensory activity in response to hypoxia (0% O_2, Fig. 2*C*). Together, these results support the notion that hyperglycemia does not trigger carotid body activation nor potentiates the responses to hypoxia. We conclude that hyperglycemia is not one of the key early events involved in carotid body deregulation that promotes increased SNS activity and dysmetabolism.

METABOLIC VICIOUS CYCLE

It is generally agreed that increased SNS activity plays a role in the generation of obesity and metabolic diseases, creating a vicious cycle that culminates in the development and maintenance of cardiometabolic pathological states (26, 52). As depicted in Fig. 3, we propose that the intermittent hyperinsulinemia caused by hypercaloric diets (*step 1*) leads to overactivation of carotid bodies (42) and to a compensatory hyperadrenergic state (*step 2*) (42, 45) that compromises glucose uptake by the liver, adipose tissue, and skeletal muscle (*step 3*) (29, 30, 43, 45, 48), increases hepatic glucose output, and increases the concentration of free fatty acids in plasma (*step 4*). Free fatty acids further compromise insulin action (*step 5*), contributing to the gradual rise in plasma glucose (4, 41). As a consequence, the pancreas secretes more insulin to counteract transient hyperglycemia, contributing to enhanced insulin signaling at the carotid bodies and to the metabolic vicious cycle. Our hypothesis has been corroborated by experimental data (42, 45) that shows that a high-fat diet increases both carotid body and SNS activity (Fig. 4). We have demonstrated that rats subjected to 3 wk of a high-fat diet exhibited increased basal minute ventilation and increased response to ischemic hypoxia, assessed by means of occlusion of the common carotid artery (Fig. 4*A*), increased basal CSN activity (Fig. 4*B*), and an increase in carotid body dopamine content (Fig. 4*C*) (42). Additionally, we showed that these animals presented an overactivation of the SNS, demonstrated by the increased low frequency-high frequency ratio obtained by power spectral analysis of heart rate variability (Fig. 4*D*) and by the increase in plasma and adrenal medulla norepinephrine and epinephrine content (Fig. 4, *E* and *F*, respectively) (42, 45). Note also that CSN resection normalizes sympathetic activity in high-fat animals (Fig. 4), confirming that the overactivation of carotid bodies is involved in a vicious cycle that involves increased sympathetic activity leading to insulin resistance and to the disruption of glucose homeostasis.

ALTERNATIVE THERAPEUTIC APPROACH

The global burden of metabolic diseases continues to increase (23, 56a), accentuating the need for novel therapeutic approaches with mechanistic approaches different from the existing in the market. Surgical blockade of CSN activity may be an interesting therapeutic strategy for early Type 2 diabetes patients or for patients who do not achieve proper glycemic control with the pharmacological options currently available in the market. However, surgical CSN resection, besides being invasive, can produce side effects related to the loss of the peripheral hypoxic response, with decreased sensitivity to CO_2 (11, 53), impaired response to exercise (14, 18, 19), and fluctuations in blood pressure (35). New types of treatments that allow precise modulation of the signaling patterns generated by the CSN would offer significant advantages to patients (6, 17), by providing long-term control of the disease, combined with significantly fewer side effects. As bioelectronic medicines emerge, the idea of an electronic device placed on the CSN that could be used to normalize the increased activity of specific CSN fibers avoiding systemic effects becomes closer to reality. This approach would bring significant improvement in the standard of care for Type 2 diabetes, requiring minimally invasive procedures and negligible interference with daily activities (6, 17). Along with this idea, we have recently demonstrated that the neuromodulation of CSN using kilohertz high frequency alternating current through cuff electrodes surgically placed on the CSN restores metabolic homeostasis in Type 2 diabetes rats (44). These beneficial effects of the neuromodulation of CSN activity on glucose homeostasis

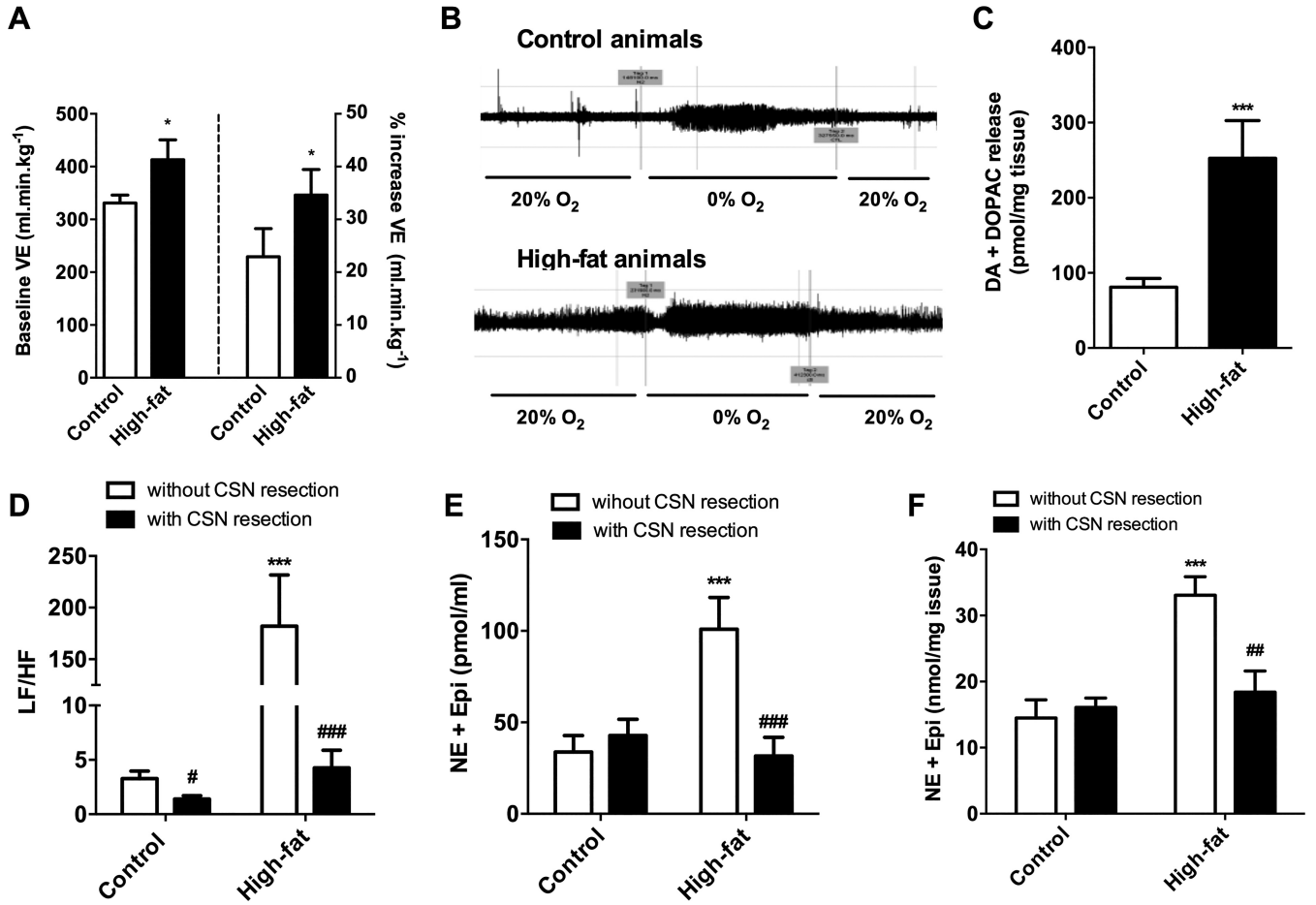

Fig. 4. Overactivation of carotid body and sympathetic nervous system produced by high-fat diet and its reversal by carotid sinus nerve (CSN) resection. *A, B,* and *C* show, respectively, the effect of high-fat diet on spontaneous and ischemic hypoxic-induced ventilation, on basal and hypoxic evoked activity of CSN, and on the release of catecholamines from the carotid body evoked by hypoxia (5% O_2). The effect of high-fat diet and of CSN resection on the sympathetic activity assessed by low frequency-high frequency (LF/HF) ratio (*D*) obtained by the spectral analysis of the heart rate and on plasma (*E*) and adrenal medulla (*F*) catecholamine content. Ventilation is represented as minute ventilation ($\dot{V}_E$) obtained by the product of respiratory frequency and tidal volume. Ischemic hypoxia was obtained by the occlusion of common carotid artery for 5 s. High-fat animals were developed by submitting Wistar rats to 3 wk of 60% lipid-rich diet. Data represent means ± SE. Student's *t*-test and 2-way ANOVA with Bonferroni multicomparison tests; $*P < 0.05$, $***P < 0.001$ control vs. high-fat diet animals; $\#P < 0.05$, $\#\#P < 0.01$, $\#\#\#P < 0.001$ animals without CSN resection vs. animals with CSN resection. DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; NE, norepinephrine; Epi, epinephrine.

and insulin sensitivity were reversed after discontinuation of the electrical stimulus (44). Together, our results put in place the necessary tools to support a potential bioelectronic medicine-based therapeutic approach for Type 2 diabetes.

CONCLUDING REMARKS

Glucose-sensing properties of the carotid bodies have been debated in the literature for almost 30 yr (3). Currently, evidence supports the notion that carotid bodies do not sense glucose directly but have a fundamental role both in glucose homeostasis and in the pathogenesis of metabolic diseases. Although not responding directly to low blood glucose, in acute hypoglycemic states carotid bodies regulate the counter-regulatory response and appropriate increase in ventilation. In metabolic diseases states, hyperinsulinemia, rather than hyperglycemia, appears to be the key trigger for CB overactivation. Much more than a plain glucose sensor, the carotid body materializes as a peripheral node that integrates information on metabolic, cardiovascular, and respiratory status, representing a natural target for therapeutic intervention in chronic diseases.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.V.C., J.F.S., and M.P.G. conceived and designed research; S.V.C., J.F.S., and M.P.G. performed experiments; S.V.C., J.F.S., and M.P.G. analyzed data; S.V.C., J.F.S., and M.P.G. interpreted results of experiments; S.V.C., J.F.S., and M.P.G. prepared figures; S.V.C., J.F.S., and M.P.G. drafted manuscript; S.V.C., J.F.S., and M.P.G. edited and revised manuscript; S.V.C., J.F.S., and M.P.G. approved final version of manuscript.

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